REMARKS

Claims 17-21 are currently pending. By the present communication, no claims have been added or canceled, and claims 17, 18, and 20 have been amended to define Applicants' invention with greater particularity. Support for the amendments can be found throughout the application as filed. Specifically, the amendments find support in, for example, original claims 4 and 7 as filed, and at, for example, page 3, lines 23-27 of the specification as filed, which discloses,

> ...even if virus vectors capable of contact infiltration of the present invention is used to infect tumor cells at a tumor site and only a part of the cells are directly infected, noninfected cells adjacent to the infected cells can be infected with the vectors through contact infiltration...,

at page 7, lines 9-13 of the specification as filed, which discloses,

> As an embodiment of the present invention, Figure 9 shows the processes of infecting target cells with a Sendai virus complex in which the M gene is deleted or inactivated and infiltrating the RNA of the present invention into surrounding non-infected cells through contact infiltration.,

at page 8, lines 24-28 of the specification as filed, which discloses,

> The wild type forms infective virus particles and causes contact infiltration, while the mutant is not able to form infective particles but introduces its genome into non-infected surrounding cells only by contact infiltration.,

and at page 16, lines 3-7 of the specification as filed, which discloses,

> However, F and HN proteins are expressed on the cell surface, and cell fusion occurs mediated by these proteins, so that virus genome can be transferred into surrounding cells. In this way, it is possible to realize virus propagation without budding (Figure 9).

As such, the claim amendments do not raise any issues of new matter, since they are fully supported by the specification as filed. Accordingly, claims 17-21 will be under consideration.

Rejection under 35 U.S.C. §112, First Paragraph

Applicants respectfully traverse the rejection of claims 17- 21 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office Action alleges that,

> while literal support in the specification for a claimed limitation is not required, some support for said claimed limitation must be present. Applicants' arguments that detection of the foreign gene must have been made because Example 6 demonstrates this detection is not persuasive. Example 6 does not demonstrate "[d]etecting the presence of the **foreign gene** (emphasis added) in the second cell", only detecting the size and shape of plaques formed by M deletion (or defect) type cDNAs. While the plaques formed by the M deleted (or defective) viral DNAs are a characteristic of cells wherein viral DNA is replicating, merely observing plaque size and shape is not equivalent to detecting the presence of a **foreign gene** transferred to a second cell. (Office Action, paragraph bridging pages 2 and 3).

Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claims 17 and 18 to require detecting fusion of cells contacted with the first cell, rendering the objection moot. Withdrawal of the rejection is respectfully requested.

However, in so far as the rejection may apply to the amended claims, Applicants respectfully submit that it is widely accepted in the field of virology that the detected plaque is indicative of viral spreading from the first infected cell to neighboring cells. As is known in the art, viral populations do not grow through cell division, because they are acellular; instead, they use the machinery and metabolism of a host cell to produce multiple copies of themselves. Thus, the spread of the virus means the spread of the viral genome. Furthermore, since the foreign gene is integrated in the viral genome, the spread of the virus also means the spread of the foreign gene. As such, Applicants respectfully submit that detection of the spread of the plaque is equivalent to detection of the presence of the foreign gene.

The Action further alleges that,

> with regard to the argument that the specification need not disclose conventional techniques, it is noted that the claims recite detection of the foreign gene transferred to a second cell and hence said detection methodology is essential subject matter. Essential

> subject matter must be present in the specification (unless incorporated by reference to a US patent or US patent publication which does not itself incorporate essential subject matter by reference) and applicants cannot argue that it would have been obvious for the skilled artisan to use any (undisclosed) detection method for determining the presence of **a foreign gene transferred specifically into a second cell**. (Office Action, page 3).

As discussed above, Applicants have amended claims 17 and 18 to require detecting fusion of cells contacted with the first cell, rendering the objection moot. However, in so far as the rejection may apply to the amended claims, Applicants respectfully submit that the test for written description is whether "newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." (M.P.E.P. §2163 I-B). Since the virus has the foreign gene in its genome, plaque formation in the second cell is necessarily indicative of the presence of the foreign gene in the second cell. Accordingly, the newly added claim limitation was supported in the specification through express, implicit, or inherent disclosure. Furthermore, Applicants note that an argument based on the added claim limitation being "obvious" was never presented. In contrast, Applicants merely argued that the claim limitation is supported in the specification through express, implicit, or inherent disclosure, since one of ordinary skill in the art would have been able to select from a plethora of conventional techniques for differentiating the second cell from the first.

The Action further alleges that,

> The claimed limitation of "detecting a foreign gene" reads on a genus of detection methods, i.e. detecting a marker or reporter gene transferred to a second cell, detecting a therapeutic gene by detection of beneficial effect on the second cell to which the gene is delivered, etc. Applicants provide no disclosure on detection of transfer of a specific foreign gene to a second cell from the first infected cell. (Office Action, page 3).

As discussed above, Applicants have amended claims 17 and 18 to require detecting fusion of cells contacted with the first cell, rendering the objection moot. However, in so far as the rejection may apply to the amended claims, Applicants respectfully submit that regardless of whether the foreign gene is a marker, reporter, or therapeutic gene, the presence of the foreign gene can be detected by the expansion of cell fusion, as required by the amended claims.

Finally, the Action alleges that,

> the claims read on detecting the presence of the foreign gene specifically in the second cell and not in the first cell. This encompasses situations in which there is no fusion between the first and second cells and the cells remain separate. The instant specification provides no disclosure of detection methods which would discriminate between the two cells and detect a specific foreign gene transfer from the first cell to the second. (Office Action, paragraph bridging pages 3 and 4).

As discussed above, Applicants have amended claims 17 and 18 to require detecting fusion of cells contacted with the first cell, rendering the objection moot. However, in so far as the rejection may apply to the amended claims, Applicants respectfully submit that transfer of the gene wherein the cells remain separate is outside the claimed scope since the original claim reads on "a method of transferring a foreign gene ... *through contact infiltration*" (emphasis added). The claim also had a limitation of "allowing the first cell to *contact* the second cell" (emphasis added). Applicants respectfully direct the Examiner's attention to the page 16, lines 3-5 of the specification as filed, which teaches, "F and HN proteins are expressed on the cell surface, and *cell fusion occurs* mediated by these proteins, so that virus genome can be transferred into surrounding cells." (emphasis added). Accordingly, Applicants submit that the claimed invention does not encompass situations in which there is no fusion between the first and second cells and the cells remain separate.

For the reasons provided above, Applicants submit that the claimed invention complies with the written description requirement, and request withdrawal of the rejection.

Rejection under 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 17-21 under 35 U.S.C. §103(a) as allegedly being unpatentable over Magai et al. (hereinafter, "Magai") in view of Zhang et al. (hereinafter, "Zhang") or Nable et al. (hereinafter, "Nable"). The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385), modified the standard for establishing a prima facie case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or

suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The Office Action alleges that,

> It is clear from the disclosure of Magai et al. that the complexes recited therein are deficient in disseminative capability in that cells containing said complexes are incapable of producing infectious virus particles but that the cells are capable of transferring a transgene from the infected cell to a neighboring cell by contact." (Office Action, paragraph bridging pages 5 and 6).

Applicants respectfully submit that Magai describes that "M, F and HN are components necessary for constructing the viral structure." (Magai, page 5, line 34 of EP 0 864 645 A1). Magai further describes that ""the gene related to the disseminative capability" refers to any one of the M, F and HN genes." (Magai, page 8, line 39). However, Magai fails to disclose that the cells comprising a Sendai virus RNA expressing viral proteins other than M protein *"are capable of introducing the transgene to a neighboring cell by contact."*

The Action further alleges that the cells comprising the complex of Magai,

> are not capable of producing virus (See Fig. 1C in Magai et al.) but the complex is capable of expressing the F protein as well as the HN protein, etc. and hence the infected cells are capable of introducing the transgene contained in the complex to a neighboring cell by contact through fusion of the infected cell and neighboring cells mediated by the expressed F protein." (Office Action, page 6).

Applicants respectfully submit that it is not clear to the Applicants how one of skill in the art, in view of Magai, would have understood that the expressed F protein mediates the transfer of the transgene to a neighboring cell by contact.

The Action further alleges that,

> Given the presence of the Sendai F and HN genes in the contemplated RNA complexes, the ordinary skilled artisan would have known that the host cells comprising said complex would be able to fuse with neighboring cells by virtue of the expressed Sendai virus F and HN proteins and hence transfer the transgene to the neighboring cell(s)" (Office Action, page 6).

Applicants respectfully submit that it is not clear to the Applicants how one of skill in the art, in view of Magai, would have understood that the host cells comprising said complex would be able to fuse with neighboring cells. As previously argued, Magai is absolutely silent with regard

to the ability of a specific species of virus to expand the transgene from the infected cell to the neighboring cell through cell-to-cell contact (*i.e.,* contact infiltration). Rather, Magai expressly describes that, "[s]ince said complexes can replicate *only within infected cells* but not spread *from cell to cell*, these techniques are especially useful in the fields of gene therapy, etc. wherein therapeutical safety is highly appreciated." (Magai, page 15, lines 3-4, emphasis added). As such, Applicants maintain that Magai teaches away from the present invention.

Applicants respectfully submit that Magai is absolutely silent with regard to the suggestion that a non-segmented (-)RNA virus, which lacks a gene encoding M protein or comprises an inactivated gene encoding M protein is incapable of transferring its genome by infectious particles but is capable of transferring its genome by contact infiltration. Applicants further submit that both Zhang and Nabel are equally silent with regard to suggesting that a non-segmented (-)RNA virus which lacks a gene encoding M protein or comprises an inactivated gene encoding M protein is incapable of transferring its genome by infectious particles but is capable of transferring its genome by contact infiltration. Accordingly, since the combined references do not teach each and every limitation of the amended claims, *prima facie* obviousness of the invention over Magai, Zhang, or Nable, either alone or in combination, has not been shown by the Office. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In summary, for the reasons set forth herein, Applicants respectfully submit that the claims clearly and patentably define the invention, and allowance of the claims is respectfully requested. If the Examiner would like to discuss any issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $405.00 as payment for Request for Continued Examination fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-identified docket number.

Respectfully submitted,

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